OBSTETRICS

The effect of maternal sleep-disordered breathing on the infant's neurodevelopment

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OBJECTIVE: We sought to examine the effect of maternal sleep-disordered breathing (SDB) on infant general movements (GMs) and neurodevelopment.

STUDY DESIGN: Pregnant women with uncomplicated full-term pregnancies and their offspring were prospectively recruited from a community and hospital low-risk obstetric surveillance. All participants completed a sleep questionnaire on second trimester and underwent ambulatory sleep evaluation (WatchPAT; Itamar Medical, Caesarea, Israel). They were categorized as SDB (apnea hypopnea index >5) and controls. Infant GMs were assessed in the first 48 hours and at 8-11 and 14-16 weeks of age. At 12 months of age the Infant Developmental Inventory and the Brief Infant Sleep Questionnaire were administered.

RESULTS: In all, 74 women and their full-term infants were studied. Eighteen (24%) women had SDB. Mean birthweight was 3347.1 ± 423.9 g. Median Apgar score at 5 minutes was 10 (range, 8—10). In adjusted comparisons, no differences were found between infants born to mothers with SDB and controls in GM scores in all 3 evaluations. Low social developmental score was detected at 12 months in 64% of infants born to SDB mothers compared to 25% of infants born to controls (adjusted $P = .036$; odds ratio, 16.7). Infant snoring was reported by 41.7% of mothers with SDB compared to 7.5% of controls ($P = .004$).

CONCLUSION: Our preliminary results suggest that maternal SDB during pregnancy has no adverse effect on neonatal and infant neuromotor development but may affect social development at 1 year.

Key words: fetal outcome, neurodevelopment, pregnancy, sleep-disordered breathing

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Pregnancy is associated with significant changes in sleep with a large proportion of pregnant women experiencing some form of sleep disruption. Physiologic and hormonal changes that occur during pregnancy, particularly during the third trimester, place women at risk for developing sleep-disordered breathing (SDB).[1,2] Indeed, SDB is common during pregnancy and self-reported snoring has been observed in up to 46% of pregnant women.[3-6] The term "sleep-disordered breathing" refers to a spectrum of abnormal respiration during sleep that ranges from primary (habitual) snoring to obstructive sleep apnea syndrome. It is characterized by episodic complete or partial obstruction of the airway during sleep, disruption of normal ventilation, intermittent hypoxemia, and sleep fragmentation.

It has been suggested that SDB during pregnancy may adversely influence the maternal and fetal well-being. Specifically, associations between SDB during pregnancy and gestational diabetes, hypertension and pre-eclampsia,[7-15] fetal growth restriction, prematurity, cesarean delivery, and low Apgar scores have been reported.[15-22] However, these observations have thus far been inconclusive, one of the reasons being that most of the published literature is based on subjective assessment of sleep and lacks objective sleep measures.

Despite this inconsistency, in a recent study we found that maternal snoring was associated with enhanced fetal erythropoiesis and elevated cord interleukin 6.[23] We therefore hypothesized that maternal SDB with the resultant subtle intermittent hypoxia could influence the developing fetal brain.

To our knowledge, there are no reports on the effect of maternal SDB on infant neurodevelopmental status despite the ostensibly large body of data regarding the association of pediatric SDB with attention deficit, hyperactivity, and emotional and behavioral disturbances.[24-31] For all these reasons, we designed a prospective study using an

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objective sleep study measure to investigate the effects of maternal SDB on their infants. We hypothesized that infants born to mothers with SDB will exhibit lower developmental scores.

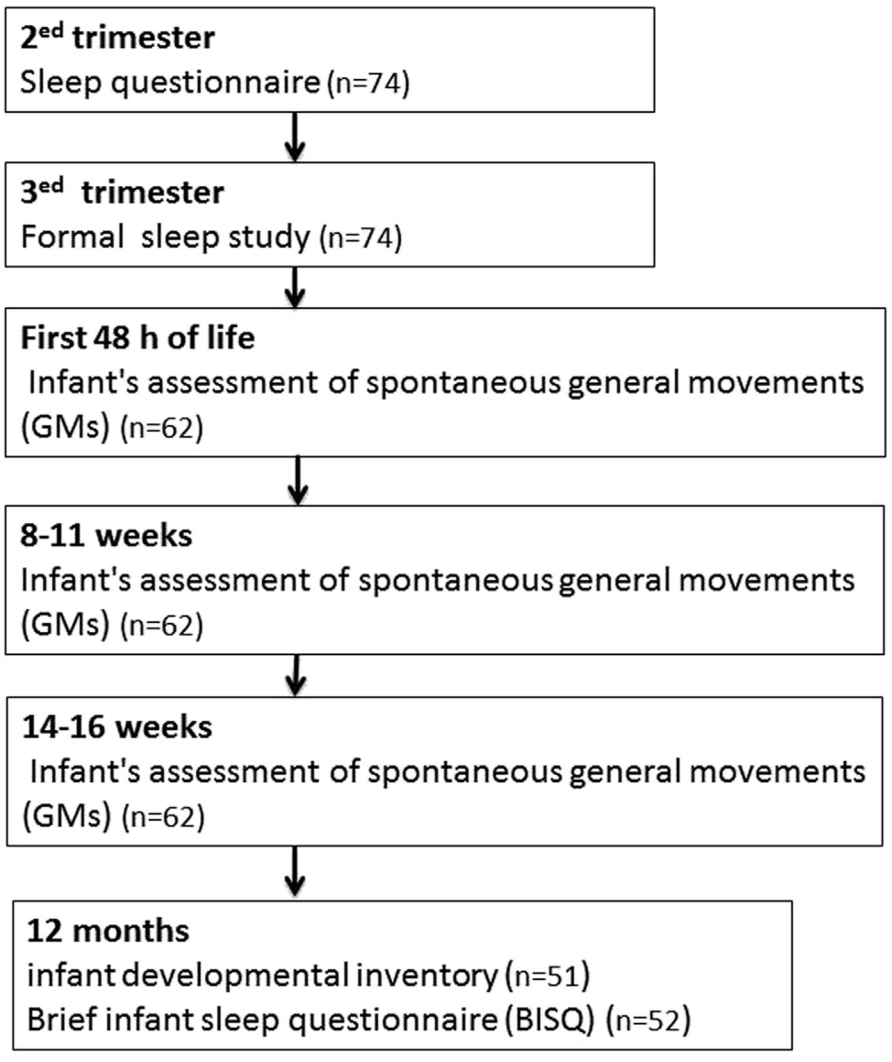
Our aims were to determine the effect of maternal SDB on neonatal and infant spontaneous general movements (GMs) and developmental outcome at 1 year.

Materials and Methods

Women in the third trimester of a singleton, uncomplicated pregnancy who attended low-risk obstetric surveillance from March 2009 through March 2012 were recruited. All participants completed a sleep questionnaire during the second trimester and underwent a sleep study during the third trimester of pregnancy. Infant GMs were assessed during the first 4 months of life. Development and sleep questionnaires were administered at 12 months. The study design and recruitment flowchart are presented in the Figure.

The study was approved by the institutional review board. The study was registered at ClinicalTrials.gov (NCT00931099). Informed consent was obtained from all participants.

FIGURE
Recruitment flowchart



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Maternal and infant data

All women completed a sleep questionnaire (gestational week 25-27) regarding the presence of habitual snoring before and during pregnancy. Habitual snoring was defined as snoring at least 3 nights per week.[32,33] Pregnancy-onset snoring was considered present when habitual snoring began during pregnancy. All participants underwent an ambulatory overnight sleep study between 33-36 weeks of gestation using a validated ambulatory sleep technology (WatchPAT 200; Itamar Medical, Caesarea, Israel).[34-37] Apnea hypopnea index, respiratory disturbance index, oxygen desaturation index, mean oxygen saturation (SpO2) and SpO2 nadirs were retrieved as previously described.[37] Women with an apnea hypopnea index >5 per hour of sleep were considered to have SDB.[38] We used the standard adult criteria for SDB, since there is no distinctive threshold for SDB in pregnancy. Medical records review was conducted by one of the researchers blinded to the sleep study results. Pertinent demographic (sex, gestational age, birthweight) and clinical (mode of delivery, Apgar scores at 1 and 5 minutes, and any perinatal complications) information were collected.

Outcome data

Spontaneous GMs assessment of infants

GMs were videotaped (15 minutes in length) for offline assessment in the first 48 hours of life, between 8-11 weeks of age, and between 14-16 weeks of age postterm. All infants were dressed in a diaper only, and were in the supine position. During off-time replay of the 3 periods videotaped, the GM quality was analyzed and assessed by an independent trained observer and the data scored. GMs were scored when infants were in active wakefulness. Periods of crying, fussing, and sucking were excluded from analysis.[39,40] The observer was unaware of the infant's group assignment (maternal SDB yes/no) as well as of other test results and clinical data.

Sleep evaluation at the age of 1 year

Sleep was evaluated at 1 year of age using the Brief Infant Sleep Questionnaire

(BISQ). The BISQ is a validated sleep questionnaire assessing the infant's typical sleep patterns based on parental reports.[41] A yes/no question regarding snoring at the age of 1 year was added to the BISQ.

Socioeconomic status

The modified, 2-factor index Hollingshead scale was used for determining the infant's socioeconomic status. The maternal and paternal scores were averaged.[42]

Developmental questionnaire at the age of 1 year

At 1 year of age the developmental level was evaluated using the Infant Developmental Inventory questionnaire.[43,44] This screening instrument is a parental report of the infant's developmental skills in 5 areas (gross motor, fine motor, social, self-help, and language). The instrument shows age-appropriate standards from which an estimated developmental age was recorded for each subdomain. An estimated developmental age, divided by the infant's chronological age, and multiplied by 100, yielded the subdomain developmental quotient. Averaging all 5 subdomains yields a total score for general developmental function, also expressed as developmental quotient.

Statistical analysis

The statistical analyses were performed with software (SPSS, version 19.0; IBM Corp, Armonk, NY). Comparisons of variables were conducted between infants born to women with SDB (study group) and infants born to non-SDB mothers (controls). Comparisons of variables according to group assignment were performed with independent *t* tests for continuous variables, and the χ^2 analyses for categorical variables. Linear and logistic regression analyses were performed for several dependent variables and were adjusted for the following confounders: gestational age, birthweight, sex, 5-minute Apgar score, and socioeconomic status. All reported *P* values are 2-tailed with statistical significance set at $P < .05$.

TABLE 1
Comparison of maternal and newborns characteristics and maternal sleep measures of study group (sleep-disordered breathing) and controls

Characteristic	SDB (n = 18)	Controls (n = 56)	*P* value
Maternal			
Age, y	33.1 ± 3.7	32.7 ± 4.6	.78
BMI prepregnancy	25.3 ± 4.3	21.9 ± 2.5	.005
Delivery			
Normal	14 (78%)	42 (75%)	.95
Cesarean	3 (17%)	11 (20%)	
Instrumental	1 (6 %)	3 (5%)	
Gravida, median (range)	2.0 (1.0–7.0)	2.0 (1.0–5.0)	.84
Para, median (range)	2.0 (1.0–3.0)	1.0 (1.0–3.0)	.13
Total sleep time, min	334.4 ± 58.0	344.0 ± 83.0	.60
Respiratory disturbance index	14.4 ± 5.7	6.1 ± 3.2	< .0001
Apnea hypopnea index	11.2 ± 5.1	1.3 ± 1.4	< .0001
Oxygen desaturation index	3.1 ± 1.9	0.3 ± 0.4	< .0001
Mean SpO2	94.7 ± 0.9	96.1 ± 0.9	< .0001
SpO2 nadir	89.6 ± 2.3	93.1 ± 2.2	< .0001
Newborn			
Male sex	10 (56%)	35 (63%)	.64
Apgar 1, median (range)	9 (4–9)	9 (3–9)	.14
Apgar 5, median (range)	10 (8–10)	10 (9–10)	.85
Gestational age, wk	39.3 ± 1.4	39.2 ± 1.4	.13
Birthweight, g	3371.0 ± 454.6	3356.7 ± 419.9	.9
Cord PH	7.28 ± 0.08	7.29 ± 0.09	.81

BMI, body mass index; *SDB*, sleep-disordered breathing; *SpO2*, oxygen saturation.

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RESULTS

In all, 74 healthy women completed a sleep questionnaire and underwent ambulatory sleep evaluation. Infant spontaneous GMs and 1-year developmental inventory were administered to 62 and 51 subjects, respectively (Figure). We were unable to obtain complete outcome data in all infants due to unavailability of parents or investigators. The demographic characteristics of the 23 children with a missing 1-year developmental inventory were similar to those with a complete developmental questionnaire (mean gestational age: 39.4 ± 1.3 vs 38.9 ± 1.3, $P = .14$, and mean birthweight: 3391.3 ± 393.4 vs 3284.8 ± 464.4 g, $P = .35$). No participants had maternal or pregnancy-related complications such as hypertension, gestational diabetes, infection, or fetal growth restriction. Twenty-nine (39%) women reported habitual snoring. Ten (13%) were habitual snorers before and during pregnancy and 19 (26%) were pregnancy-onset snorers. Eighteen (24%) women met our criteria for SDB and 56 served as a control group. Of the 18 women with SDB, 5 did not report snoring, 4 reported snoring before and during pregnancy, and 9 reported pregnancy-onset snoring by questionnaire. Except for 2 premature deliveries at 36 weeks of gestation, all infants were born at term. In all, 45 (61%) newborns were male. Comparison of maternal and newborn characteristics as well as maternal sleep measures between the

TABLE 2
Infant assessment of spontaneous general movements in first 48 hours, and at 8-11 and 14-16 weeks of age

GM	Maternal SDB (n = 17)	Controls (n = 45)	*P* value	*P* value[a]
First 48 h	14.2 ± 3.9	15.0 ± 3.7	.47	.27
8-11 wk	22.5 ± 7.8	22.8 ± 7.3	.99	.98
14-16 wk	22.9 ± 8.1	23.8 ± 6.4	.66	.37
Total score	19.1 ± 7.3	20.5 ± 5.5	.56	.19

GM, general movement; *SDB*, sleep-disordered breathing.

[a] Derived from linear regression analysis adjusted for gestational age, birthweight, sex, and Apgar score at 5 min.

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study group (SDB) and the controls are presented in Table 1.

General movements

The 3 sequential assessments of GMs were administered to 62 infants. No significant differences were found between the 2 groups before and after adjustment (Table 2).

Outcome at 12 months

The Infant Developmental Inventory questionnaire was administered at 1 year of age to 51 subjects (11 from the SDB group and 40 from the control group). As shown in Table 3, no significant differences were found in the gross and fine motor, language, and self-help developmental scores between the 2 groups. Of note, the mean social developmental scores were lower in the study group when compared to the controls and almost reached statistical significance (97.8 ± 19.7 vs 114.9 ± 28.3, $P = .067$). A social developmental score <100 was detected in 7 (64%) infants born to SDB mothers compared to 10 (25%) controls (adjusted $P = .036$; odds ratio, 16.7).

Sleep measures derived from the BISQ at the age of 1 year are presented in Table 4. No significant differences in nocturnal sleep duration, daytime sleep, number of nocturnal awakenings, sleep latency and wake after sleep onset, and frequency of problematic sleep were found between children born to mothers with SDB compared with controls. However, infant snoring was reported by 5 of 12 (41.7%) mothers with SDB compared to 3 of 40 (7.5%) controls ($P = .004$).

COMMENT

This is the first study that investigated the effect of maternal SDB during pregnancy on neonatal and infant neurodevelopment. Our preliminary findings suggest that maternal SDB has no impact on neonatal and infant spontaneous GM. Nevertheless, despite the similar early neuromotor status, assessment at 1 year suggested that infants born to mothers with SDB exhibited lower social

TABLE 3
Developmental scores at age of 1 year

Variable	SDB (n = 11)	Controls (n = 40)	*P* value	*P* value[a]	OR
Age, mo	12.9 ± 1.6	13.0 ± 1.4	.88		
Male sex	5 (45%)	24 (60%)	.34		
Parental socioeconomic status	24.2 ± 2.8	26.9 ± 7.5	.36		
Social score	97.8 ± 19.7	114.9 ± 28.3	.067	.13	
Social score <100, n (%)	7 (64)	10 (25)	.029	.036	16.7
Self-help score	115.3 ± 9.7	115.2 ± 21.0	.93	.63	
Self-help score <100, n (%)	2 (18)	0 (0)	.13	.99	
Gross motor score	114.7 ± 31.7	115.2 ± 21.0	.95	.43	
Gross motor score <100, n (%)	4 (36)	8 (20)	.28	.11	4.5
Fine motor score	115.6 ± 21.2	115.2 ± 21.1	.95	.59	
Fine motor score <100, n (%)	1 (9)	7 (18)	.46	.54	0.47
Language score	114.7 ± 21.6	117.0 ± 19.2	.74	.57	
Language score <100, n (%)	3 (27)	5 (13)	.27	.15	6.2
Total developmental score	111.6 ± 17.4	114.3 ± 18.2	.66	.34	
Total score <100, n (%)	3 (27)	6 (15)	.39	.13	6.3

OR, odds ratio; *SDB*, sleep-disordered breathing.

[a] Derived from linear regression analysis adjusted for gestational age, birthweight, sex, Apgar score at 5 min, and parental socioeconomic status.

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TABLE 4
Brief Infant Sleep Questionnaire results at age of 1 year in infants born to mothers with sleep-disordered breathing and to controls

Variable	SDB (n = 12)	Controls (n = 40)	*P* value
Nocturnal sleep time, min	630.0 ± 54.3	594.4 ± 59.8	.07
Daytime sleep, min	146.3 ± 33.9	139.9 ± 43.6	.64
No. of night awakenings	1.83 ± 1.1	1.7 ± 1.4	.69
Wakefulness time after sleep onset, min	17.9 ± 16.6	22.1 ± 35.7	.7
Sleep latency, min	16.3 ± 7.7	21.7 ± 16.4	.14
Bedtime	8.06 pm ± 0.27	8.08 pm ± 0.36	.85
You consider your child's sleep to be a problem, n (%)	3 (25)	9 (22.5)	.85

SDB, sleep-disordered breathing.

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developmental scores and increased rate of snoring compared to controls.

To test our hypothesis on the effects of maternal SDB on the developing brain we performed 3 sequential evaluations of the neonatal and infant GMs and found similar scores in the 2 groups. We chose the GM assessment because of its good predictive ability of neurodevelopmental outcome.[45] Spontaneous GM evaluation is primarily based on neuromotor functions; therefore future studies should use behaviorally oriented evaluations to further test this hypothesis.

At 12 months of age, we administered a developmental questionnaire and found lower social developmental scores in infants born to pregnant mothers with SDB while motor and speech development were not different between the 2 groups.

Our finding supports previous observation of Hermans et al,[46] who demonstrated a significantly decreased grooming behavior and alterations in passive avoidance and locomotor activity in rat pups born of dams exposed to intermittent antenatal hypoxia. In their study, the abnormal neonatal behavior disappeared at postnatal day 30. Most neonatal neuromotor reflexes and Morris water maze performance (learning and memory testing) at 29 days were not affected by intermittent pregnancy hypoxia.[46] Gozal et al,[47] in their study of gestational intermittent hypoxia in a rat model, also found no effects on Morris water maze testing at postnatal day 30.

In a neurohistological study of intermittent gestational hypoxia in a rat model, Zechel et al[48] reported a transient delay in neuronal migration associated with alterations of multiple proteins early in the postpartum period. Based on these animal studies one could hypothesize that intermittent gestational hypoxia, increased intrathoracic pressure swings, or sleep fragmentation associated with maternal SDB could alter fetal brain developmental processes, either directly or via mediators. For example, enhanced fetal hypothalamic–pituitary–adrenal activity was found in a rat model of intermittent gestational hypoxia resulting in anxiety-like behavior in adult male offspring.[49] Other possible mediators may involve maternal and fetal perturbation of the autonomic nervous system[50] and exposure of the fetus to inflammatory mediators,[23] which ultimately may affect fetal brain development.

Nevertheless, comparison between human and animal models of maternal SDB should be viewed cautiously since the level of hypoxia applied in animal models may exceed that of human models.

Our finding of increased rate of snoring (41.7%) among infants born to mothers with SDB is in agreement with previous publications showing that family history of SDB is a risk factor for developing SDB during childhood.[51] The contribution of other risk factors such as allergy, adenotonsillar hypertrophy, and weight was not investigated in the present study. However, this study is the first to show that maternal SDB during pregnancy increases the risk for SDB in the infant and, more importantly, that snoring is already present at 1 year of age.

Given the known association between pediatric SDB and behavioral emotional impairments, attention difficulties, impulsivity, hyperactivity, and daytime sleepiness, it is possible that our findings of delayed social development in infants born to mothers with SDB are also mediated by the infants' SDB.[24-31]

Based on the nature of the neurobehavioral consequence of SDB,[52] early screening and intervention in children born to snoring mothers may potentially attenuate the progression of the neurocognitive outcomes.

This study has several limitations: our cohort consists of a relatively small number of mothers with SDB and includes some infants with incomplete outcome data that limit the ability to conduct subgroup analysis between chronic and pregnancy-onset SDB. In addition, the infants' development and sleep habits were based on a parental questionnaire and not on objective testing. Therefore, our results should be viewed as preliminary. Future studies should implement comprehensive neonatal behavioral assessments and a formal developmental outcome instrument that focuses on infants' communication. Notwithstanding such considerations, the strength of our study is its prospective longitudinal

follow-up design, utilizing a formal objective sleep study measure in a homogenous low-risk pregnancy cohort.

In conclusion, this is the first study examining the effect of gestational maternal SDB on the neonatal and infant neurodevelopment. Our preliminary results suggest that maternal SDB during pregnancy has no large adverse effect on neonatal and infant neuromotor development but it may affect social development at the age of 1 year. In addition, maternal SDB is associated with increased rate of infant snoring. Further studies using comprehensive developmental tools and larger sample size are warranted. ■

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